Tetrahedron Vol. 42, No. 6, pp. 1841 to 1844, 1986
Printed in Great Britain.

0040-4020/86 $3.00+.00

SYNTHESIS AND STRUCTURAL STUDIES OF BRIDGEHEAD DIENES

3 - OXOBICYCLO[6.3.1]DODECA - 1(11),8(9) - DIENE - (*ZZ*) - 11 - CARBOXYLIC ACID AND 3 - OXOBICYCLO[7.3.1]TRIDECA - 1(12),9(10) - DIENE - (*ZZ*) - 12 - CARBOXYLIC ACID

K. J. Shea,* L. D. Burke and Robert J. Doedens
Department of Chemistry, University of California, Irvine, CA 92717, U.S.A.

(*Received in USA* 12 *June* 1985)

Abstract—Single crystal X-ray structures of two bridgehead dienes are reported. The bridgehead double bonds of diene 7 show only modest deviation from strain-free tetrasubstituted double bonds. The double bonds in bridgehead diene 6, however, exhibit an average deviation of the C—C=C—C torsion angle ($\phi + \chi$) of 14°.

Replacement of a H atom on ethylene by some other substituent often results in a predictable change in the chemical and spectroscopic properties of the molecule. Twisting a C=C bond may be viewed as a perturbation that is also capable of producing modifications in the chemical and spectroscopic properties of the alkene. There are only limited data documenting the chemical response to torsionally distorted C=C bonds,[1] and structural studies of twisted double bonds are very scarce.[2]

A goal of our research program is to examine the relationship between chemical reactivity and structural deformations of torsionally distorted double bonds. The program requires accumulation of a body of structural data for compounds that contain double bonds of varying degrees of distortion and then relating that information to the chemical properties of these compounds. In an effort to secure structural data for bridgehead alkenes, we have utilized several synthetic entries that have been developed in our laboratory with the hope that certain derivatives of these compounds would be suitable for single crystal X-ray analysis. In this paper we describe the results of two structural studies of bridgehead dienes.

RESULTS AND DISCUSSION

Synthesis of bridgehead dienes

We have recently developed general synthetic entries into molecules that contain torsionally distorted C=C bonds.[3] One approach utilizes type 2 intramolecular Diels–Alder chemistry for the construction of 1,5-bridged-*trans*,*trans*-1,4-cycloalkadienes 1 (Eq. 1).[4] A

1 (1)

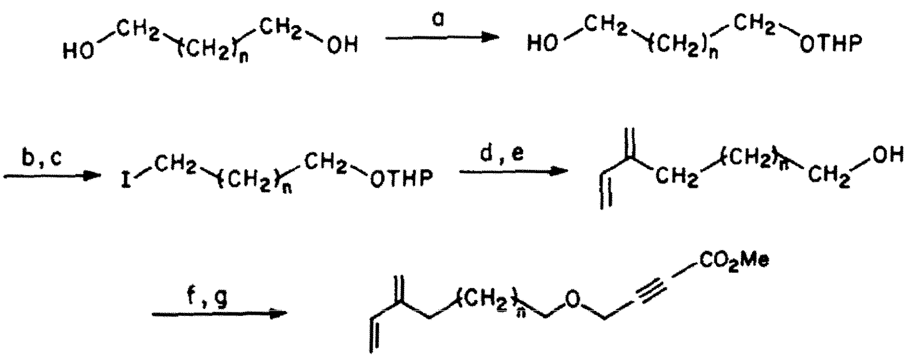
particularly attractive feature of this synthesis is that it permits simultaneous introduction of two bridgehead double bonds. Furthermore, activating groups on the dienophile are positioned to provide a handle for functionality that may permit preparation of derivatives suitable for X-ray structural work. Past experience with these intramolecular Diels–Alder cycloadditions revealed that an oxygen substituent β to the dienophile greatly facilitates the reaction.[4b] Within this constraint, dienyne esters 2 and 3 were prepared by the procedures outlined in Scheme 1.

A key step in the synthesis, coupling of a chloroprene Grignard reagent with a protected iodo-alcohol, was catalyzed by Li_2CuCl_4.[5] Following hydrolysis, the dienols were isolated in yields of 70–80%. Condensation of the Na salt of the dienols with propargyl bromide, followed by treatment with n-butyl lithium, and then methyl chloroformate affords esters 2 and 3 in a 70% yield for the two steps. Sealed tube solution phase thermolysis of dienyne ester 2 at 210° in benzene for 3.4 hr gives the bridgehead diene ester 4 in a chromatographed yield of 67%. The homologous ester 3 is considerably less reactive. Heating a benzene solution of 3 at 210° (sealed tube) for 5.5 hr returns starting material and bridgehead diene ester 5, in chromatographed yields of 21 and 33%, respectively.

Like many bridgehead dienes synthesized in our laboratory, cycloadducts 4 and 5 are not crystalline compounds. This situation was not improved by preparation of *p*-nitrobenzoyl derivatives. Simple saponification of the methyl esters however, proved to be more fruitful. Hydrolysis of bridgehead diene ester 4 with lithium hydroxide in aqueous THF gave, upon chromatography, bridgehead diene carboxylic acid 6 as a clear colorless crystalline compound, m.p. 118–120° in 40% yield. Redissolving in CH_2Cl_2 and slow evaporation returned bridgehead diene carboxylic acid 6 as X-ray quality crystalline plates. Treatment of bridgehead diene ester 5 with aqueous methanolic KOH afforded acid 7 in 71% yield. Recrystallization from CH_2Cl_2–pentanes gave plates (m.p. 114–117°) which also yielded material suitable for X-ray analysis.

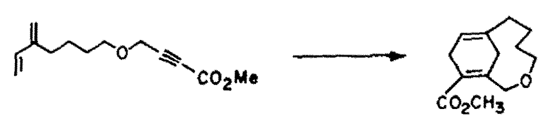
Structural studies

ORTEP plots of both bridgehead diene carboxylic acids are shown in Figs 1 and 2 (hydrogens excluded). The X-ray analysis permits unambiguous assignment of the *meta* regioisomer for both cycloadducts.[6] The



1, n = 2, 2, n = 3

Scheme 1. (a) DHP, H^+; (b) MsCl, Et_3N; (c) NaI, acetone, reflux; (d) $CH_2CHC(MgCl)CH_2$, THF, Li_2CuCl_4; (e) H_3O^+; (f) NaH, DME, $HCCCH_2Br$; (g) n-BuLi, $ClCO_2CH_3$.



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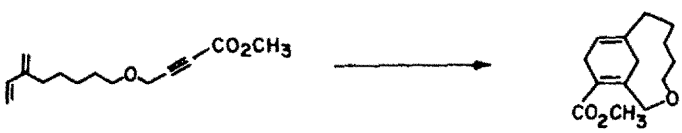

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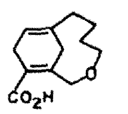

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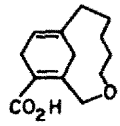

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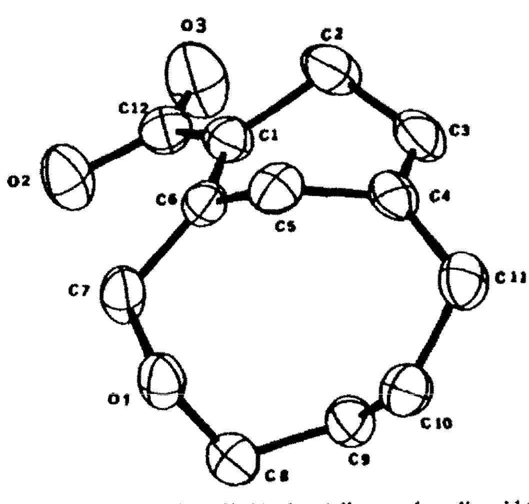


Fig. 1. ORTEP drawing of bridgehead diene carboxylic acid 6 showing the atomic numbering scheme.

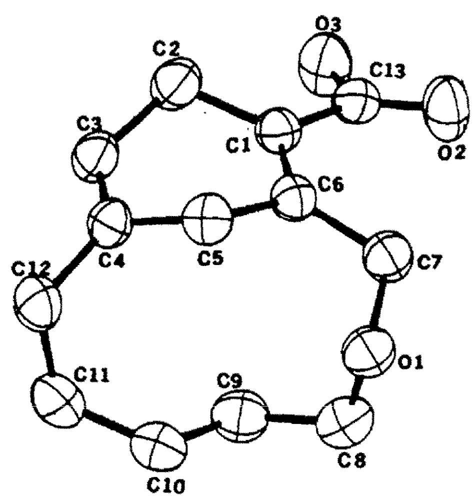


Fig. 2. ORTEP drawing of bridgehead diene carboxylic acid 7 showing the atomic numbering scheme.

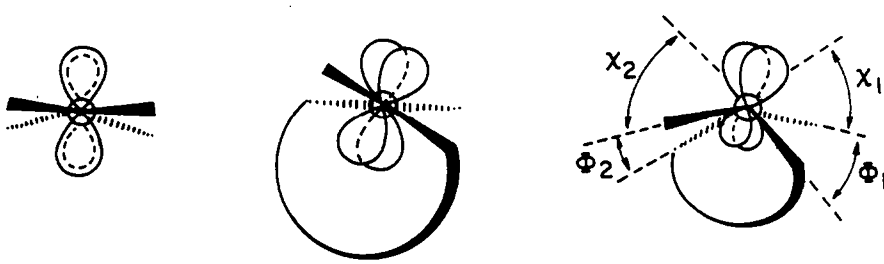
cycloadducts are bridged derivatives of *trans,trans*-1,4-cycloalkadienes. The 1,5-bridge locks the 1,4-cyclohexadiene ring into a boat conformation. The folding angle, determined by the angle of intersection between the least square planes defined by C(2)—C(3)—C(4)—C(5) and C(2)—C(1)—C(6)—C(5), is a measure of the puckering in the ring. For diene **6** this angle is 130.7°, and for the less highly strained derivative **7**, the angle is 140°. The puckering is also represented in the valence angles C(1)—C(2)—C(3) and C(4)—C(5)—C(6) in diene **6** (109.0°, 108.1°) and **7** (111.1°, 111.5°).

Both bridgehead dienes contain two torsionally distorted C=C bonds. The nature of the distortion is illustrated by the sequence of structures below. The *trans*-cycloalkene substructure tends to twist the C=C bond out of coplanarity resulting in loss of overlap of the two p orbitals. To minimize the energy of this situation it was suggested that the double bond carbons undergo rehybridization with incorporation of s character into the p orbitals.[7]

opposite C—C=C—C and C—C=C—C torsion angles are ϕ_1 and ϕ_2. The torsion (ϕ) and out-of-plane bending (χ) deformations for both bridgehead dienes are summarized in Table 1. Both χ_{a_1} and ϕ_{a_1} are omitted since they require precise location of the vinyl hydrogens at C(3).

Inspection of the data in Table 1 reveals that the double bonds in bridgehead diene **7** experience only very minor distortion. Deviations from values typical of strain-free alkenes fall within the range of 1.6–3.4°. From the structural criteria the double bonds of this bridgehead alkene are near "normal". In the homologous bridgehead diene **6**, however, we observe the onset of more significant out-of-plane distortions and pyramidalizations. As expected these distortions are quite unsymmetrical. The bridgehead carbons experience considerable pyramidalization, $\chi_{b_1} = 6.1°$ and $\chi_{a_2} = 10.1°$, while pyramidalization at the non-bridgehead carbon, $\chi_{b_1} = 1.4°$, is negligible.

A measure of the torsional distortion at C(2)—C(6) is represented by ϕ_{b_1} (the values for ϕ_{b_2} and ϕ_{a_2} are



A consequence of this rehybridization is the pyramidalization of the carbons of the double bond. The limited structural data available confirms this analysis.[2] Additional pyramidalization of the bridgehead carbons (i.e. C(4) and C(6)), is expected to result from introduction of the second carbocyclic bridge.

For each bridgehead double bond there are two deformations that describe the distortion. The first is pure twisting or torsion ϕ (deviation from coplanarity of the two p type orbitals) and the second, an out of plane bending (χ), which is a measure of the extent of rehybridization or pyramidalization at the sp^2 carbons. The independent geometrical parameters that are necessary to completely define the non-planar distortions in dienes **6** and **7** are shown in the figure. The angles formed by the single bonds emanating from the sp^2 carbons are χ_1 and χ_2 and they measure the extent of out-of-plane deformations at each sp^2 center. The

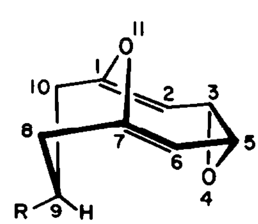
constrained by the boat cyclohexane substructure). In bridgehead diene **7** this value is 3.0° while in **6** the olefin torsion angle is 12.3°. Thus the average deviation of the C—C=C—C torsion angle from 180° ($\phi+\chi$) is 14° for **6** and only 4.5° for **7**. Finally, despite substantial distortions at the bridgehead carbons of diene **6**, there are no anomalies in the bond angles or bond distances within the chain of atoms spanning carbons C(4) and C(6).

From the above analysis we may conclude that the transition between "strain free" and strained bridgehead dienes occurs in the homologous series **7** → **6**. Comparison of **6** with *syn*-oxepin oxide **8**, is instructive. The average deviation of the torsion angle in **6** ($\phi+\chi = 14°$), is less than that found in **8** (25°), a derivative of *trans,trans*-1,5-cyclononadiene.

It is hoped that the structural studies of dienes **6** and **7** will form a basis for understanding the observed chemical differences between these two molecules.

Table 1. Summary of χ and ϕ for bridgehead dienes **6** and **7**. The C(3)=C(4) and C(6)=C(1) bonds are identified as a and b, respectively

	Compound	
	6	**7**
χ_{b_1}	1.4°	1.7°
χ_{b_2}	6.1°	1.6°
χ_{a_2}	10.1°	2.4°
ϕ_{b_1}	12.3°	3.0°
ϕ_{b_2}	7.7°	3.2°
ϕ_{a_2}	2.3°	3.4°



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EXPERIMENTAL

Preparation and crystallographic data for 3 - oxobicyclo[6.3.1]dodeca - 1(11),8(9) - diene - 11 - carboxylic acid (**6**)

A THF soln (10 ml) of bridgehead diene **4**[4b] (0.541 g, 2.4 mmol) was added to an aqueous soln (3 ml) of $LiOH \cdot H_2O$

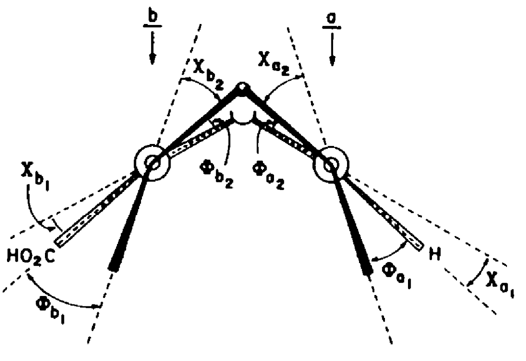

Fig. 3. Schematic representation of bridgehead diene 1 indicating pyramidalization (χ) and torsion (ϕ) at the bridgehead double bonds.

(0.2856 g, 6.8 mmol). The mixture was warmed to 40° for 20 hr and the crude product isolated by acidifying with HCl (pH 6) followed by ether extraction. Column chromatography (silica gel, 1:1 pentanes–ether) yields the bridgehead diene **6** (0.202 g, 40%) as a clear, colorless crystalline compound, m.p. 118–120°.

^{1}H-NMR (250 MHz, $CDCl_3$) δ ppm 10.0 (s, 1H, —$CO_2\underline{H}$), 5.79 (m, 1H, —C$\underline{H}$=C), 4.89 (d, J = 14.8 Hz, 1H, =C—C$\underline{H}_2$—O—), 4.39 (d, m, J = 14.8 Hz, 1H, =C—C$\underline{H}_2$—O—), 3.75 (d, d, J = 12.7, 1.7 Hz, 1H, C$\underline{H}_2$—(C=C)$_2$), 3.66 (m, 2H, CH_2—O—C$\underline{H}_2$$CH_2$, C$\underline{H}_2$—(C=C)$_2$), 3.07 (m, 1H, CH_2—O—C$\underline{H}_2$$CH_2$), 2.51 (m, 2H), 2.28 ("t", d, J = 12.7, 2.9 Hz, 1H), 2.14–1.96 (m, 2H), 1.57 (m, 2H), 1.31 (m, 1H); ^{13}C-NMR (62.89 MHz, $CDCl_3$) δ 171.8, 163.0, 144.9, 131.0, 124.5, 69.8, 68.3, 33.6, 32.9, 30.4, 27.7.

X-Ray crystal structure data: $C_{12}H_{16}O_3$, monoclinic, space group $P2_1/a$, $a = 7.383(5)$ Å, $b = 11.65(1)$ Å, $c = 13.91(1)$ Å, $\beta = 118.33(5)°$, $U = 1053(1)$ Å^3, $Z = 4$. Intensity measurements were made on a Syntex $P2_1$ diffractometer, Mo K_α radiation $\lambda K_\alpha = 0.71073$ A, graphite monochrometor. A total of 1598 reflections were collected up to $2\theta = 45°$ among which 1376 had intensities $I > 2.33\sigma(I)$, no absorption correction was made. The structure was solved by direct methods (MULTAN 80) and refined by full matrix least squares refinement to $R = 0.044$ and $R_w = 0.065$ (anisotropic thermal parameters for carbon and oxygen, hydrogen atoms experimentally determined). Tables of positional parameters, anisotropic temperature factors, bond angles, and interatomic distances are included as supplemental information.

Preparation and crystallographic data for 3 - *oxobicyclo*[7.3.1] - *trideca* - 1(12),9(10) - *diene* - (*ZZ*) - 12 - *carboxylic acid* (7)

In a similar manner bridgehead diene **5**[4b] upon treatment with KOH (3 equiv) in MeOH after 24 hr followed by acidification (HCl, pH 7) concentration and column chromatography afforded solid **7**, m.p. 114–117° in 71% yield; ^{1}H-NMR (250 MHz, $CDCl_3$) δ ppm 11.8 (brs, 1H, —CO_2H), 5.66 (d, J = 6 Hz, 1H, —C$\underline{H}$=C), 4.99 (d, J = 15 Hz, 1H, —CH_2—O), 4.29 (d, d, J = 12, 2 Hz, 1H, —C$\underline{H}_2$—O), 3.62 (m, 2H), 3.43 (d, d, d, J = 18, 7, 1.5 Hz, 1H), 3.25 (m, 1H), 2.55 ("t", 1H), 2.34)m, 2H), 2.13 (m, 1H), 1.89 (m, 1H), 1.68 (m, 1H), 1.45 (m, 3H), 1.20 (m, 1H); ^{13}C-NMR (62.89 MHz, $CDCl_3$) δ 172.3, 158.6, 142.5, 126.4, 121.8, 71.6, 69.8, 35.5, 34.1, 30.2, 29.4, 28.8, 24.9.

X-Ray crystal structure data: $C_{13}H_{18}O_3$, triclinic, space group $P\bar{1}$, $a = 8.226(5)$ Å, $b = 8.776(5)$ Å, $c = 9.650(6)$ Å, $\alpha = 121.7(5)°$, $\beta = 87.5(5)°$, $\gamma = 99.9(5)°$, $U = 583(1)$ Å^3, $Z = 2$. Intensity measurements were made in a Syntex P2, diffractometer, Mo K_α radiation $\lambda K_\alpha = 0.71073$ A, graphite monochrometor. A total of 1528 reflections were collected up to $2\theta = 45°$ among which 1376 had intensities $I > 2.33\sigma(I)$, no absorption correction was made. The structure was solved by full matrix least squares refinement to $R = 0.045$ and $R_w = 0.066$ (anisotropic thermal parameters for carbon and oxygen experimentally determined, hydrogen atoms fixed in observed positions). Tables of positional parameters, anisotropic temperature factors, bond angles and interatomic distances are included as supplemental information.

Acknowledgement—Financial support from the National Science Foundation is gratefully acknowledged.

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